

## REMARKS

This response is due on September 19, 2003, by virtue of the attached petition and fee for a one-month extension of time.

Applicants thank Examiner Forman for the two separate Examiner interviews with Applicants' representative, Nabeela R. McMillian, on August 18, 2003 and August 29, 2003, respectively. The amendments to the claims presented above were substantively discussed with the Examiner with respect to the pending rejections under 35 U.S.C. §112, first paragraph.

In view of the amendments and remarks presented herein, Applicants request withdrawal of the rejections and favorable reconsideration of the claims.

### I. Status of the Claims and Discussion of Amendments

Claims 1-11 and 37-48 were pending in the instant application at the time of the Office action and were variously rejected under 35 U.S.C. §112 first paragraph for allegedly not being described and enabled by the specification and under 35 U.S.C. §102(a) over a number of references. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

Claims 37, 38, 44 and 47 have been canceled herein, without prejudice or disclaimer. Applicants reserve the right to pursue the canceled subject matter in further continuing applications at a later date.

As suggested in the August 29, 2003 interview, Applicants have amended claims 1, and 48 to respectively remove the terms "and correlating presence or absence of said mutation in the nucleic acid to a risk of developing hereditary lymphedema," and "and determining risk of developing hereditary lymphedema from the assaying and measuring," from these two claims, respectively. Applicants consider these deleted terms as being unnecessary in view of the claim preambles and "wherein" clauses, which specify the

determination that is made according to the method fro each human subject for the risk of developing hereditary lymphedema.

The above-described amendments necessitate minor amendments of claims 3, 4, 5, 6 and 39 to ensure that the antecedent basis of these claims is correct. More particularly, claims 3, 4, 5, and 6, each have been amendment in order to remove reference to claim 37. Likewise, claim 39 has been amended to replace the term "correlating step" with the word "method," as the amendment to claim 1 removes the literal antecedent basis for the term "correlating step."

With the entry of the foregoing amendments, claims 1-11 and 39-43, and 45-46 and 48 are pending.

**II. The rejections under 35 U.S.C. §112, first paragraph for lack of enablement and lack of written description should be withdrawn.**

In the Office action dated May 19, 2003, claims 1-11 and 37-48 were rejected under 35 U.S.C. §112, first paragraph both for an alleged lack of enablement and lack of written description. Applicants' position remains that the claims of the application are directed to screening methods and not to individual, specific mutations, and that the application contains both an adequate written description and an enabling disclosure commensurate with the claims. During the interview, the Examiner advised that the rejections under 35 U.S.C. §112, first paragraph for lack of enablement and lack of written description could be obviated by removing the term "and correlating presence or absence of said mutation in the nucleic acid to a risk of developing hereditary lymphedema" from claim 1, and removing the term "and determining risk of developing hereditary lymphedema from the assaying and measuring," from claim 48 of the application.

Applicants have implemented these amendments in accordance with the Examiner's suggestion and believe that all of the claims are now free of any rejections under 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the rejections be withdrawn.

**III. The rejections under 35 U.S.C. §102(a), should be withdrawn in view of the accompanying declarations from Dr. Robert Ferrell, which establish that none of the documents are proper 35 U.S.C. §102(a) references.**

Claims 1-2, 4-10, 37-40 and 42-47 stand variously rejected as allegedly anticipated by the disclosure of Lawrence *et al.* (*American Journal of Human Genetics*, 63(4), Abstract 1053, A185 (1998); hereafter "Lawrence *et al.*"), Kimak *et al.* (*American Journal of Human Genetics*, 63(4), Abstract 180, A185 (1998); hereafter "Kimak *et al.*"), and Witte *et al.*, (*Lymphology*, 31:145-155, (1998); hereafter Witte *et al.*)

**a. Claims 1-2, 4-10, 37-40 and 42-47 of the present invention are patentable over Lawrence *et al.***

In the Office action dated May 19, 2003, claims 1-2, 4-10, 37-40 and 42-47 were alleged to be anticipated by the disclosure of Lawrence *et al.* However, Lawrence *et al.* describes the work of the instant Applicants, and was published less than one year before the effective filing date of the instant application.

A Declaration Under 37 C.F.R. § 1.132 of Dr. Robert Ferrell (hereafter "second Ferrell Declaration") filed herewith establishes that, to the extent the Lawrence *et al.* publication discloses or suggests aspects of subject matter being claimed, such disclosure, or suggestion is the work of co-applicants Ferrell and Finegold. In fact, to the extent Lawrence *et al.* discloses or suggests a complete invention of any particular claim, it is an invention of Ferrell and Finegold (see paragraphs 3 and 4 of the second Ferrell Declaration).

Lawrence *et al.* does not, in fact, disclose or suggest all aspects of the present invention. For example, there is no disclosure of functional effects of Flt4 mutations reported in the paper. As Dr. Ferrell states in the second Ferrell Declaration, characterization of such function was a contribution that came from co-inventors Alitalo and Karkkainen (see paragraphs 3 and 5 of the second Ferrell Declaration.) To the extent that one or more claims embody this aspect of the invention, such claims are not anticipated by Lawrence *et al.*

Therefore, the rejections under 35 U.S.C. §102(a) based on Lawrence *et al.*, should be withdrawn.

**b. Claims 1-2, 4-10, 37-40 and 42-47 of the present invention are patentable over Kimak *et al.***

In the Office action dated May 19, 2003, claims 1-2, 4-10, 37-40 and 42-47 also were alleged to be anticipated by the disclosure of Kimak *et al.* However, Kimak *et al.* also describes the work of the instant Applicants. The Kimak *et al.* abstract has a listed publication date of October 1998, and as such, may be removed as effective prior art if the work described therein was the work of the instant Applicants.

The second Ferrell Declaration establishes that, to the extent the Kimak *et al.* publication discloses or suggests aspects of subject matter being claimed, such disclosure, or suggestion is the work of co-applicants Ferrell and Finegold (see paragraphs 3 and 5 of the second Ferrell Declaration.) In fact, to the extent Kimak *et al.* discloses or suggests a complete invention of any particular claim, it is an invention of Ferrell and Finegold.

Kimak *et al.* does not, in fact, disclose or suggest all aspects of the present invention. For example, there is no disclosure of functional effects of Flt4 mutations reported in the paper. As Dr. Ferrell states in the Declaration filed herewith, characterization of such function was a contribution that came from co-inventors Alitalo and Karkkainen (see paragraphs 3 and 6 of the second Ferrell Declaration.) To the extent that one or more claims embody this aspect of the invention, such claims are not anticipated by Kimak *et al.* Therefore, the rejections under 35 U.S.C. §102(a) based on Kimak *et al.*, should be withdrawn.

**c. Claims 1-2, 4-10, 37-40 and 42-47 of the present invention are patentable over Witte *et al.***

Claims 1-2, 4-10, 37-40 and 42-47 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by the disclosure of Witte *et al.* Applicants respectfully traverse the rejection.

Initially, Applicants submit the present claimed invention is not disclosed in Witte *et al.* However, regardless of the merits of the disclosure of Witte *et al.*, Applicants submit that the Witte *et al.* reference should not be considered effective prior art because the instant Applicants performed the work of the present invention prior in time to the publication of the Witte *et al.* reference.

Filed herewith is a Declaration Under 37 C.F.R. § 1.131 of Dr. Robert Ferrell in Response (referred to hereafter as "the third Ferrell Declaration"). Where a reference is cited that discloses only part of the claimed invention, the affidavit under 37 C.F.R. §1.131 is required to show no more than the reference shows. (see MPEP 715.02 citing *In re Stryker*, 435 F.2d 1340 (CCPA 1971)).

Witte *et al.* ostensibly is directed to phenotypic and genotypic heterogeneity in familial Milroy lymphedema, an autosomal dominant disorder, which is admitted by the authors of that paper as having phenotypes that are "not well described, and the genomic location and functional expression of the gene or gene(s) underlying this and related familial lymphedema syndromes remains largely unknown." Witte *et al.* proceeded to attempt linkage analyses to localize the gene for ML. To guide them in this work the authors "specifically examined the suggested linkage to the vascular endothelial growth factor (VEGF)-C receptor (Flt4) gene." (See abstract). A closer review of the description of the subjects and methods used by Witte *et al.* reveals that the "suggested linkage to the" VEGF-C receptor Flt4 came from the disclosure of Kimak *et al.* (See page 147, second column, second paragraph). Witte merely performed linkage studies to localize the gene for ML to 5q34-q35, *i.e.*, the locus to which Flt4 maps, and discusses this gene in the context of the disclosure of Kimak *et al.* Witte *et al.* provides no further teachings relevant to the invention than what the present inventors had already taught and published in Kimak *et al.*

Prior to Witte *et al.*, Kimak *et al.*, taught linkage and mutation in the Flt4 gene in hereditary lymphedema and concluded that Flt4 plays a critical role in the development of lymphedema, and identified specific mutations in Flt4 in families with hereditary lymphedema. Witte *et al.* does not provide a teaching of any other mutations in

Flt4. In fact, Witte teaches away from aspects of the invention by predicting (incorrectly) that the mutations first described by Kimak are "gain of function mutations" (Witte *et al.*, at p 154, col. 1).

Thus, for the purposes of 35 U.S.C. §102(a), the relevant disclosure of Witte *et al.* is less than what is first taught in Kimak *et al.* This is insufficient to establish anticipation of the present claims. As Dr. Ferrell states in the third Ferrell Declaration, and as discussed above, to the extent the Kimak *et al.* publication discloses or suggests aspects of subject matter being claimed, such disclosure, or suggestion is the work of co-applicants Ferrell and Finegold. The Kimak *et al.* abstract shows that co-Applicants Ferrell and Finegold had conceived, and reduced to practice, those aspects of the present invention before October 1998. The Witte *et al.* paper was not published until December of 1998. The only relevant portion of the Witte *et al.* disclosure to the claims of the present application is a disclosure that arose out of Kimak *et al.* Therefore, the rejections under 35 U.S.C. §102(a) based on Witte *et al.*, should be withdrawn.

In summary, Applicants submit that it is clear that all of the claims of the present invention are free of the prior art. As such, Applicants respectfully request that the rejection of claims 1-2, 4-10, 37-40 and 42-47 under 35 U.S.C. §102(a) based on Lawrence *et al.*, Kimak *et al.*, and Witte *et al.* be withdrawn and the claims be reconsidered for allowance.

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#### IV. Conclusions

Applicants believe that all of the rejections have been overcome and the claims of the instant application are now in condition for allowance and request an early indication of such a favorable disposition of the case. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

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Respectfully submitted,

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